REMARKS

In response to a Restriction Requirement mailed June 15, 2005, Applicants elected to prosecute the method claims of **Group VIII** without traverse. In the instant Office Action, the Examiner has raised two issues, which are set forth by number in the order they are addressed herein:

1) Claims 25-54 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement; and
2) Claims 25, 27, 28, 30-33, 35-41, 43, 44 and 46-54 stand rejected under 35 U.S.C. 102(b) as allegedly anticipated by Birkett (U.S. Patent No. 6,231,864).

Applicants have canceled Claims 25-55 and entered new Claims 56-116, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments. Applicants reserve the right to prosecute the original, similar, or broader claims in one or more future application(s).

Applicants wish to thank the Examiner and Supervisor for the courteous interview conducted on January 9, 2006 and the helpful comments provided therein. Applicants' Interview Summary is attached to this paper.

In response to the outstanding Office Action, Applicants submit the following:

1) The Claims Are Enabled

The Examiner has rejected Claims 25-54 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner states:

> The breadth of the claims provides that (i) the modified hepatitis core antigen ("core antigen") is capable of producing particles despite the insertion or substitution of one or more acidic amino acids, and (ii) the core antigen may be derived from any hepatitis virus (Office Action, page 3).

The Examiner states that the specification fails to provide directions on how to substitute and/or insert acidic amino acids in a core antigen and fails to teach insertion points for other viruses such as HCV.

Although Applicants respectfully disagree that the claims lack enablement, Applicants have canceled Claims 25-55 and have entered new Claims 56-116, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments, and while reserving the right to prosecute the original, similar, or broader claims in one or more future application(s). Specifically, Applicants have added new Claims 56-116, which are directed to methods of making modified hepadnavirus core antigens and nucleic acids encoding these antigens. Support for the new Claims 56-116 can be found throughout the specification and the original claims (e.g., *see* Example 15, including Tables 17 and 18, as well as, original Claims 25-30). Accordingly, the new claims require that the modified core antigens are members of the "family of DNA-containing viruses that cause hepatitis (inflammation of the liver) in a wide range of vertebrate species" (Specification, at page 34, lines 10-15), for instance, HBV and HBV-like viruses of woodchuck, ground squirrel, and duck but not hepatitis A virus or non-A, non-B hepatitis viruses. Applicants respectfully submit that the entire scope of claims 56-116 is fully enabled.

Further direction in this regard is provided in Claims 56-68 and 90-101, by inclusion of the limitation "adding nucleotides that encode an acidic amino acid to said first nucleic acid **to reduce said isoelectric point below 7.0**" as discussed in the Interview conducted on January 9, 2006. Support for this amendment is found in the teaching that "positively charged inserts (e.g., pI equal to or greater than 7.0) appear to [have] adversely affected assembly of hybrid WHcAg or HBcAg particles" (Specification, at page 109, lines 17 and 18). Moreover, Table 17 lists 10/11 epitopes with a pI greater than or equal to 7.0 that fail to assemble as hybrid particles, and lists 9/9 epitopes with a pI less than 7.0 that are capable of assembling as hybrid particles.

Claims 69-89 and 102-116, include the limitation "adding nucleotides that encode an acidic amino acid to said second nucleic acid at a position **within an immunodominant loop** of said hepadnavirus core antigen or **within an alpha-helix adjacent to said immunodominant loop**." Support for this amendment is found in the teaching that "in reference to a hepadnavirus core antigen, the term 'loop' refers to a portion of the hepadnavirus core antigen which links the second and third alpha-helices and which contains an immunodominant B cell epitope" (Specification, at page 36, lines 14-16). Moreover, Figure 3 provides a schematic of a hepadnavirus core antigen depicting positions within the immunodominant loop (e.g., residues

76-82) and within each of two alpha-helices adjacent to the immunodominant loop (e.g., residues 50-75 and 83-110), that tolerate insertion of heterologous antigens.

During the Interview of January 9, 2006, the Examiner and Supervisor expressed concern that one of skill in the art would not appreciate the residues of the hepadnavirus core antigens that could be mutated without detrimental effect. In an effort to expedite the allowance of this application, Applicants have limited the claims to modifications of the hepadnavirus core antigens and nucleic acids encoding these compositions, which occur within regions that the Applicants have found to be tolerant of insertions. (*See discussion supra).*

Applicants also want to point out that support for the contention that hepadnavirus core antigens were sufficiently characterized at the time the instant application was filed to permit one skilled in the art to make and use the invention of Claims 69-89 and 102-116, without undue experimentation, given the present disclosure, is also provided by the electron cryomicroscopy studies of Bottcher et al., Nature, 386:88-91 (1997), previously supplied to the office (and from whom Figure 3 has been adapted). U.S. Patent No. 6,231,864 to Birkett (cited in the instant Office Action) also provides guidance:

> strategic modifications of HBc is an insert mutation of the HBc protein. ... The insert is provided to the region about 50 to about 100 of the hepatitis B core protein sequence shown in SEQ ID NO:2. The preferred region of the insert corresponds to the hepatitis B core protein immunodominant loop region at about amino acid residue 70 to about 90 (Birkett, column 4, lines 11-22).

Accordingly, Applicants request that the rejections for lack of enablement be withdrawn and respectfully submit that the Examiners' concerns as to the positions on the hepadnavirus core antigen that would support modification should be satisfied.

2) The Claims Are Novel

The Examiner has rejected 25, 27, 28, 30-33, 35-41, 43, 44 and 46-54 under 35 U.S.C. 102(b) as allegedly anticipated by Birkett (U.S. Patent No. 6,231,864). The Examiner states "Birkett discloses a method of producing a carrier protein, wherein the carrier protein comprises a hepatitis B core protein having an insert of 1 to 40 amino acids, and wherein the insert is derived from an antigenic protein of a pathogen" (Office action, page 5). Although, Applicants respectfully disagree with the Examiner's position, Applicants have canceled Claims 25-55 and

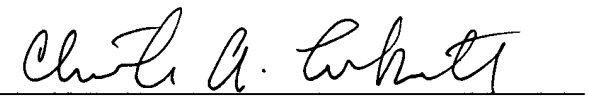
entered new Claims 56-116, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments, and while reserving the right to prosecute the original, similar, or broader claims in one or more future application(s).

In particular, new Claims 56-116 all require "determining the isoelectric point of said heterologous antigen encoded by said first nucleic acid and, if said heterologous antigen is determined to have an isoelectric point greater than or equal to 7.0, adding nucleotides that encode an acidic amino acid" to said first or said second nucleic acid. As discussed in the Interview conducted on January 9, 2006, Birkett fails to teach or suggest determining the pI of any sequence. Accordingly, Applicants respectfully request that the novelty rejections be withdrawn.

CONCLUSION

Applicants believe the arguments and amendments set forth above traverse the Examiner's rejections and place the application in a condition for allowance and such action is earnestly solicited. If, however, any unresolved issues remain, the Examiner is cordially invited to contact the undersigned so that these matters can be addressed in an expeditious manner.

Dated: February 16, 2006

By: 

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